Poster Title	Author(s) and Affiliations(s)	Topic Area
Building an Adverse Outcome Pathway Network for Arsenic-Induced Diabetes	Ingrid L. Druwe1, J. Allen Davis2, Jeff Gift1, Ila Cote1, Janice S. Lee1 EPA, Office for Research and Development, National Center for Environmental Assessment â€“ Research Triangle Park, 2 EPA, Office for Research and Development, National Center for Environmental Assessment â€“ Cincinnati;	Methods for assimilating and using mechanistic information to support evidence synthesis and integration
Development and application of â€œkey characteristics of male reproductive toxicantsâ€for screening and sorting mechanistic evidence	Xabier Arzuaga1, Erin Yost1, Andrew Hotchkiss1 Brandy Beverly2, Catherine Gibbons1, Martyn T. Smith3, Niels E. SkakkebÃ¦k4, Russ Hauser5, Rodrigo L. Pagani6, Steve Schrader, Lauren Zeise7, Gail S. Prins8 1U.S. Environmental Protection Agency, National Center for Environmental Assessment; 2National Institute of Environmental Health Sciences, National Toxicology Program; 3University of California, Berkeley, School of Public Health; 4Department of Growth & Reproduction, University of Copenhagen; 5Harvard University, T.H. Chan School of Public Health; 6University of Illinois Health, Department of Urology; 7California Environmental Protection Agency; Office of Environmental Health Hazard Assessment; 8University of Illinois at Chicago, College of Medicine.	Approaches and tools to search and screen the literature for mechanistic data

The key characteristics of carcinogens as an organizing principle for exploring mechanistic evidence: ethylene oxide as a case study	Jason M. Fritz1, Nagu Keshava2, Suryanarayana V. Vulimiri2, Catherine Gibbons3. 1US EPA, OECA/OCEFT/NEIC; 2US EPA, ORD/NCEA-Washington; 3US EPA, ORD/NCEA-IRIS	Practical experience with implementing systematic reviews of mechanistic evidence into human health assessments
Enhancing the Consistent Interpretation of Mechanistic Evidence via Systematic Review: Assisted Semantic Ontology Concept Mapping	Michelle Angrish1, Gail Hodge2, Sean Watford3,4, George Woodall1, and Anand Mudambi5 1National Center for Environmental Assessment, US EPA, RTP, Durham, NC, 27711 2Information International Associates, Oak Ridge, TN, 37830 3National Center for Computational Toxicology, US EPA, RTP, Durham, NC, 27711 4Oak Ridge Associated Universities, Oak Ridge, TN, 37830 5Office of the Science Advisor, US EPA, Washington DC, 20460	Methods for assimilating and using mechanistic information to support evidence synthesis and integration

A case study approach to systematically review mechanistic information of the thyroid hormone adverse outcome pathway	Andrea Kirk1 , Kristan Markey2, Isabelle Lee3, Pamela Noyes4, Nancy Baker5, Seema Schappelle2, and Stanley Barone2. 1 Office of Land and Emergency Management, Environmental Protection Agency 2 Office of Chemical Safety and Pollution Prevention, Environmental Protection Agency 3 University of Pennsylvania, Perelman School of Medicine 4 Office of Research and Development, Environmental Protection Agency 5 Leidos, Inc.	Practical experience with implementing systematic reviews of mechanistic evidence into human health assessments
Using Mechanistic Evidence to Support the Biological Plausibility of Cardiovascular Effects following PM2.5 Inhalation	Michael J. Stewart, Ellen Kirrane, Michelle Angrish, Jennifer Nichols Office for Research and Development, National Center for Environmental Assessment Research	Methods for assimilating and using mechanistic information to support evidence synthesis and integration

Implementing machine learning methods in literature searching and screening to identify and categorize mechanistic evidence	Jennifer L. Nichols, Ryan Jones, Michael J. Stewart, and Steven J. Dutton EPA, Office for Research and Development, National Center for Environmental Assessment Research	Approaches and tools to search and screen the literature for mechanistic data

Abstract

Arsenic exposure has been associated with numerous diseases including various cancers, adverse pregnancy outcomes, and metabolic diseases such as diabetes mellitus, however, the exact molecular events by which arsenic contributes to these diverse disease states is yet to be fully elucidated. In their recommendations to the IRIS Program regarding the inorganic arsenic assessment, the National Research Council (NRC) recommended conducting mode of action (MOA) analysis to facilitate understanding of exposure-response relationships and interindividual variabilities for health outcomes where dose response extrapolation to below the observed range may be necessary (NRC, 2013). The AOP framework (Villenueve et al., 2014) was used to organize and identify important key events and data gaps in the arsenic-induced diabetes MOA. To identify the key events leading to the AO, we performed a literature search in PubMed and identified peer reviewed medical reviews of idiopathic diabetes disease. We screened the results and included publications that described mechanisms and or molecular events in the onset of idiopathic diabetes mellitus disease. We assembled the AOP for idiopathic diabetes by binning the results into key events in the disease process. Next, we performed a targeted literature search for arsenic MOA and used clustering to identify and tag AOs using studies from the previous IRIS arsenic assessments as seeds. We took the information under the diabetes tag and overlaid the information onto the AOP for idiopathic diabetes disease. This allowed us to identify key events in the progression of iAs-induced diabetes. While this approach has been helpful in identifying key mechanistic steps and illustrates a process whereby mechanistic information can be systematically arrayed to help inform human health risk assessments, the analysis was not sufficient to dictate a dose-response shape. However, the results from this analysis helped to refine the scope of the assessment, focusing it on the relevant epidemiologic studies.

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Since the introduction of ten key characteristics of carcinogens as a basis for organizing mechanistic data on carcinogenesis, the National Academy of Sciences has recommended that key characteristics approaches also be developed for noncancer hazards. The aim of this project was to identify a set of key characteristics that can be used for searching, screening, and sorting mechanistic evidence on chemical-induced toxicological responses in the male reproductive system. An expert workgroup was convened at the University of California-Berkeley in March 2018 to review the key characteristics approach and determine whether it can be applied to endocrine disruptors and male and female reproductive toxicants. For male reproductive toxicants, eight key characteristics were identified based on survey of established mechanisms, and include alterations in: 1) germ cell functions, 2) somatic cell functions, 3) reproductive hormone levels/production, 4) hormone receptors, 5) DNA damage, 6) epigenetic modifications, 7) oxidative stress, and 8) inflammation. As a proof of principle, this set of key characteristics was used to organize mechanistic evidence from in vivo and in vitro studies on the PCB mixture Aroclor 1254 and effects in the male reproductive system. The proposed key characteristics of male reproductive toxicants facilitates the systematic screening of mechanistic data from diverse research methods, models, and endpoints, as well as from a variety of known pathways for chemical-induced toxicity that can support hazard characterization. Disclaimer: The views expressed are those of the authors and do not necessarily represent the views or policies of the US EPA.

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In 2016, the U.S. Environmental Protection Agency's Integrated Risk Information System Program finalized a cancer assessment of ethylene oxide (EtO), characterizing it as "carcinogenic to humans" following inhalation exposure. EtO induces lymphoid and breast cancers in both humans and rodents, as well as other tumors in rats and mice. While strong epidemiological evidence was instrumental in the human health hazard characterization process, evaluation of the animal and mechanistic data was also critically important. Core concepts from the key characteristics of carcinogens (KCCs) (Smith et al., 2016), a pragmatic means of categorizing and evaluating the weight of evidence for mechanisms of carcinogenesis, were adopted in the organization of the mechanistic data summary sections supporting the mode of action analysis. In subsequent work, the mechanistic evidence identified in the comprehensive literature search included in the IRIS assessment has been further reviewed and organized in a systematic manner using the KCCs as an organizing principle, coupled with a weight of evidence approach and integrated into adverse outcome pathways. Strong and consistent evidence indicates that EtO is both electrophilic and mutagenic, representing two of the 10 KCCs; however, evidence for oxidative stress, another KCC, was neither strong nor consistent. Evidence of coherence in genetic or genomic damage in similar tissues across rodents and humans provides further support, linking relevant associations across data streams. One significant challenge was a paucity of mechanistic data identified from the EtO assessment literature search to support evaluation of 7/10 of the KCCs; specific supplemental literature searches have since been performed to locate published information pertinent to each KCC. In this case study of EtO, the evaluation and discussion of cancer mechanisms was facilitated by using the key characteristics of carcinogens as a central organizing principle to evaluate mechanistic data.

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As part of implementing systematic review, the US Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) program extracts data from ~150 studies per year across 15–20 chemical assessments that are in the development phase. These data are stored in the Health Assessment and Workspace Collaborative (HAWC, https://hawcprd.epa.gov/about/) a free, open-source, and web-based application. Data extraction of author reported health findings have introduced a data consistency and semantic challenge because terms reported by authors are inconsistent (e.g. cytotoxicity, cell death, programmed cell death, cell viability). Inconsistent language may lead to duplication and/or misinterpretation of study findings, make it difficult to efficiently retrieve information from HAWC, and pose a significant barrier to data exchange across different databases used to store toxicity findings. To address these data inconsistencies, the author reported terms managed within EPA HAWC were matched to ontologies and ontology classes within Bioportal (https://bioportal.bioontology.org/ (a comprehensive repository of medical ontologies) to create a controlled vocabulary and ontology useful for expressing relationships between terms. The results (between the input [author term] and Bioportal ontology classes) were scored as: 1 = perfect match, 0.5 = synonym, and other values (0–1) for partial matches. The matching process returns other parameters (e.g. ontology, preferred name, synonym, class definition, class parent, parent definitions) that were used along with the numerical score to annotate author terms into a HAWC controlled vocabulary. The controlled vocabulary is critically important to unify study data managed by the HAWC database, whereas ontologies are used to query the database for relationships between those terms. The result is increased transparency and consistency in identifying and retrieving pertinent evidence during evidence synthesis. The EPA HAWC vocabulary and ontology are interoperable with other databases such as the Adverse Outcome Pathway (AOP) knowledge base and by class matching and ontology mapping can be integrated and used for advanced querying of potential relationships between exposure and outcome.

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The US Environmental Protection Agency's (EPA) uses systematic review (SR) and systematic evidence mapping for multiple purposes including elucidation of biological pathways and identification of reference chemicals for model and test guideline evaluation. SRs use well-defined, transparent, consistently applied approaches to evaluate available research on a topic.

We have adapted and built upon standard systematic review frameworks (such as NAS/IOM6, OHAT7, and TSCA8) to interrogate complex biological pathways and mechanisms. The proposed approach is expected to facilitate and further refine efforts to design SR approaches for interrogation of mechanistic lines of evidence.

Early search strategies of the thyroid literature identified 1+ million potentially relevant articles across a broad range of biological complexity. These results prompted the need to adapt and develop workflows that integrate elements of evidence mapping together with data extraction, machine learning systems and natural language processing, and harmonization of ontologies for management and optimization of large scale pathway-based systematic reviews. Given the breadth and complexity of the literature space, key innovations include modularizing the workflows, inventorying the study elements and experiments rather than papers, and tracking data extraction against inventories. It is unlikely that the complete literature space could ever be surveyed by a single research entity.
This adapted framework is being piloted to support the development of high throughput screening strategies to interrogate thyroid perturbations by:

-Identifying molecular mechanisms of xenobiotic disruption of thyroid hormone-related networks;
-Identifying new potential high and low throughput test methods for further development and evaluation of molecular initiating events of adverse outcome pathways; and
-Identifying diverse reference chemicals with a range of potencies.

We anticipate that this approach will generate evidence roadmaps of downstream adverse outcome key events. We present a conceptual model, adapted systematic review framework, and preliminary results of interrogating mechanistic information of thyroid hormone perturbation pathways.

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National Ambient Air Quality Standards (NAAQS) are set for the six criteria pollutants: particulate matter (PM) ozone (O3), oxides of sulfur, oxides of nitrogen, lead, and carbon monoxide. Primary NAAQS are set to protect public health- including sensitive populations such as children, older adults and people with chronic diseases. The Integrated Science Assessments (ISAs) identify, evaluate, and synthesize the best available and most policy-relevant exposure and health evidence, and communicate critical science judgments regarding the extent to which a specific health effect is related to exposure to a specific criteria pollutant. In making causality determinations, it is important to provide evidence that can plausibly link the inhalation of a criteria pollutant to downstream health effects that are systemic in nature. In the 2018 ISA for PM, a new and innovative approach was taken to systematically assess the biological plausibility for epidemiologic results indicating positive associations between ambient PM2.5 concentrations and serious health outcomes such as ischemic heart disease, heart failure, and mortality. This approach leveraged mechanistic animal toxicology evidence along with human health endpoint data to create biologically plausible pathways by which inhalation exposure to PM2.5 could lead to these health outcomes. Here, we describe this approach and these biologically plausible pathways, placing emphasis on the role of mechanistic data in their construction. We also briefly describe how this process has been improved upon in the O3 ISA by incorporating elements of systematic review.

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The National Ambient Air Quality Standards (NAAQS) for criteria air pollutants are established by the EPA as mandated by the Clean Air Act to protect public health and welfare. A critical component in reviewing the NAAQS is the development of the Integrated Science Assessments that assess the state of the science informing the relationship between ambient exposures and a range of health and welfare effects. This requires that EPA scientists identify, evaluate, and integrate a broad range of scientific evidence, including mechanistic evidence that is an important aspect to understanding the nature of the relationship between exposure and effect. Because of the vast amount of evidence pertinent to ISAs from both observational and experimental studies, identifying and evaluating the relevant evidence in a comprehensive and efficient manner is a challenge. In the current review of the Ozone NAAQS, recently initiated under an accelerated timeline by directive from the EPA Administrator, methods and approaches for ISA development have been streamlined and modernized to further adopt systematic review methodologies, including for the identification and categorization of mechanistic evidence. As presented in this case study, a combination of machine learning and automated approaches in literature searching through the Health and Environmental Research Online database and the adoption of the SWIFT-ActiveScreener tool, have resulted in a substantially more efficient process to identify and categorize evidence. Ultimately, this streamlined workflow provides an easily adaptable process to effectively search and screen for mechanistic evidence that is a critical component to drawing conclusions in scientific assessments supporting key Agency policy decisions.

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